

WHAT IS CLAIMED IS:

1. An artificially produced peptide which neutralizes a biological activity of interleukin-18, comprising a part or the whole of the amino acid sequences of variable regions in an anti-interleukin-18 antibody.
2. The peptide of claim 1, wherein the anti-interleukin-18 antibody is a monoclonal antibody.
3. The peptide of claim 1, wherein the anti-interleukin-18 antibody is against human or mouse interleukin-18 as antigen.
4. The peptide of claim 1, which suppresses inflammation induced by the biological activity of interleukin-18.
5. The peptide of claim 1, wherein the variable regions comprise the amino acid sequences of SEQ ID NOs:1 and 2.
6. The peptide of claim 1, which comprises a part or the whole of the amino acid sequences of complementarity determining regions in the variable regions.
7. The peptide of claim 1, which comprises a part or the whole of the amino acid sequences of SEQ ID NOs:3 to 8.
8. The peptide of claim 1, which has an amino acid sequence selected from the group consisting of SEQ ID NOs:9 and 10.
9. The peptide of claim 1, which is in the form of a humanized antibody.

10. The peptide of claim 1, wherein the interleukin-18-neutralizing activity of said peptide per antigen-binding site is substantially equivalent to that of the parental antibody.

11. A composition comprising as an effective ingredient the peptide of claim 10 and a pharmaceutically acceptable carrier.

12. A method to treat a living body for preventing, alleviating, or remedying a disease selected from the group consisting of asthma, graft-versus-host disease, rheumatoid arthritis, and sepsis, said method comprising administering an effective amount of the composition of claim 11 to the living body.

13. A method to treat a living body in need of autoimmunity, immunosuppressive, or anti-inflammatory treatment, said method comprising administering an effective amount of the composition of claim 11 to the living body.

14. The peptide of claim 1, wherein the interleukin-18-neutralizing activity of said peptide per antigen-binding site is not lower than that of an immunoglobulin molecule comprising the amino acid sequences of SEQ ID NOs:1 and 2 as the light and heavy chain variable regions respectively.

15. A composition comprising as an effective ingredient the peptide of claim 14 and a pharmaceutically acceptable carrier.

16. A method to treat a living body for preventing, alleviating, or remedying a disease selected from the group consisting of asthma, graft-versus-host disease, rheumatoid arthritis, and sepsis, said method comprising administering an effective amount of the composition of claim 15 to the living body.

17. A method to treat a living body in need of autoimmunity, immunosuppressive, or anti-inflammatory treatment, said method comprising administering an effective amount of the composition of claim 15 to the living body.

18. The peptide of claim 1, which comprises, as parts of the variable regions in an anti-interleukin-18 antibody, the complementarity determining regions in the light and heavy chain variable regions, wherein not more than 30% of the amino acids of each complementarity determining region are optionally replaced by different amino acids.

19. The peptide of claim 1, wherein said variable regions are of the same antibody molecule.

20. The peptide of claim 1, wherein each of the amino acid sequences comprising a part or the whole of the variable regions in an anti-interleukin-18 antibody exhibits the interleukin-18-neutralizing activity when linked with the amino acid sequence of SEQ ID NO:1 or 2 via a suitable linker in a single chain polypeptide.

21. The peptide of claim 1, which comprises as a light chain variable region the amino acid sequence of SEQ ID

NO:1 or a fragment thereof and as a heavy chain variable region the amino acid sequence of SEQ ID NO.2 or a fragment thereof, wherein each of said fragments exhibits the interleukin-18-neutralizing activity when linked with the amino acid sequence of SEQ ID NO:1 or 2 via a suitable linker in a single chain polypeptide.

22. A DNA which codes for the peptide of claim 1.

23. The DNA of claim 22, which comprises a part or the whole of a nucleotide sequence selected from the group consisting of SEQ ID NOs:11 and 12 and their complementary sequences.

24. The DNA of claim 22, which comprises a part or the whole of a nucleotide sequence selected from the group consisting of SEQ ID NOs:13 to 18 and their complementary sequences.

25. The DNA of claim 22, which has a nucleotide sequence selected from the group consisting of SEQ ID NOs:19 and 20 and their complementary sequences.

26. The DNA of claim 22, wherein at least one nucleotide is replaced by different nucleotide, on the basis of genetic degeneracy, without changing the amino acid sequence encoded thereby.

27. The DNA of claim 22, which is inserted into an autonomously replicable vector.

28. The DNA of claims 22, which is introduced into a host selected from the group consisting of animal, plant, and microbial hosts.

29. A process of producing a peptide comprising allowing a DNA that codes for the peptide of claim 1 to express and collecting the expressed peptide.

30. The process of claim 29, wherein the peptide is collected by one or more techniques selected from the group consisting of salting out, dialysis, filtration, concentration, separatory sedimentation, ion-exchange chromatography, gel filtration chromatography, absorption chromatography, isoelectric-focusing chromatography, hydrophobic chromatography, reversed phase chromatography, affinity chromatography, gel electrophoresis, and isoelectric-focusing electrophoresis.

31. A process of preparing a peptide according to claim 1, comprising:

(a) preparing cells that produce antibodies against IL-18 consisting of the amino acid sequence of SEQ ID NO:21 or 22;

(b) cloning cDNAs for light and heavy chain variable regions from the antibody-producing cells prepared in step (a);

(c) constructing DNAs coding for single chain variable region fragments (scFvs) comprising a part or the whole of each cDNA cloned in step (b);

(d) expressing scFvs from the DNAs constructed in step (c);

(e) testing the scFvs expressed in step (d) on IL-18-neutralizing activity per antigen-binding site in comparison with an immunoglobulin molecule comprising the amino acid sequences of SEQ ID NOs:1 and 2 as the light and heavy chain variable regions respectively;

(f) selecting a DNA expressing an scFv that exhibits IL-18-neutralizing activity per antigen-binding site at a level not lower than that of the immunoglobulin molecule in step (e);

(g) constructing a DNA coding for scFv or humanized antibody as a peptide according to claim 1 with the DNA selected in step (f) and optionally with a foreign DNA, and inserting said constructed DNA into a vector;

(h) expressing the scFv or humanized antibody from the vector prepared in step (g); and

(i) collecting the scFv or humanized antibody from the resulting mixture of step (h).

32. A process of preparing a pharmaceutical composition for a disease selected from the group consisting of asthma, graft-verus host disease, rheumatoid arthritis, and sepsis, said process comprising:

(a) mixing a physiologically acceptable carrier with the peptide of claim 1 as an effective ingredient; and

(b) formulating the resulting mixture into a formula suitable for medicating a living body.

33. An agent for susceptible diseases, which comprises the peptide of claim 1 as an effective ingredient.

34. An agent of claim 33, which further comprises a pharmaceutically acceptable carrier.

35. A method to treat a living body for preventing, alleviating, or remedying a disease selected from the group consisting of asthma, graft-versus-host disease, rheumatoid arthritis, and sepsis, said method comprising administering an effective amount of the agent of claim 34 to the living body.

36. A method to treat a living body in need of autoimmunity, immunosuppressive, or anti-inflammatory treatment; said method comprising administering an effective amount of the agent of claim 34 to the living body.

37. The agent of claim 33, which contains as a stabilizer one or more members selected from the group consisting of albumin, saccharides, and buffers.

38. The agent of claim 33, which is as an agent for auto-immune diseases.

39. The agent of claim 33, which is an immunosuppressant.

40. The agent of claim 33, which is an anti-inflammation agent.

41. An interleukin-18 neutralizer, which comprises the peptide of claim 1 as an effective ingredient.

42. A method of neutralizing interleukin-18, which comprises allowing the peptide of claim 1 to act on interleukin-18.

43. An interleukin-18 inhibitor, which comprises the peptide of claim 1 as an effective ingredient.

44. A method of inhibiting interleukin-18, which comprises allowing the peptide of claim 1 to act on interleukin-18.